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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,897	05/24/2000	H. Robert Horvitz	01997/198007	5616

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/577,897	Applicant(s) HORVITZ ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,16 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6* is/are allowed.

6)☒ Claim(s) *5,16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detaied action* .

DETAILED ACTION

1. Response and Amendment filed 1-31-02 has been received.

2. Amendments to claims 5 and 6 and to the specification have been entered.

3. Claims 5, 6, 16, and 19 are pending in the instant application.

4. The new paper copy and the CRF of the Nucleotide Sequence And/Or Amino Acid Sequence have been entered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 5, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated ced-3 protein from a nematode, wherein the nematode is a Caenorhabditis elegans, C.briggsae, and C.vulgaris and wherein the protein is encoded by a ced-3 nucleic acid of a Caenorhabditis elegans, C.briggsae, or C.vulgaris, does not reasonably provide enablement for an isolated protein encoded by any and all ced-3 nucleic acids, a hydrophilic and serine rich region containing protein encoded by a nucleic acid structurally related to the ced-3 nucleic acid of SEQ ID NO 18 or a protein encoded by a nucleic acid that is functionally related to the ced-3 nucleic acid wherein the protein encoded by the nucleic acid causes cell death and a protein encoded by a nucleic acid that is both structurally and functionally related to the ced-3 nucleic acid or any other embodiments, for reasons of record set forth in the previous office action of 11-16-01. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 1-31-01 have been fully considered but they are not persuasive. Applicants have listed and addressed 6 bases of rejections. Applicants argue that they teach that a ced-3 nucleic acid would be hydrophilic in nature and would have serine rich domain. However, the hydrophilic nature of ced-3 is not a specific characteristic because if not all most proteins would have this characteristic. Likewise, serine rich domain is not a specific to ced-3 either, rather would be a common feature in proteins. It is noted that any serine kinase would have these characteristics. Searching Pubmed database with these characteristics (serine rich and hydrophilic and protein) resulted in over 40 references, however when apoptosis was added to the search terms, no reference was retrieved. This clearly indicates that serine rich domain and hydrophilic nature are not specific to ced-3 proteins. Applicants arguments that they don't disclose only the C. elegans ced-3 protein, rather have disclosed ced-3 of C. briggsae and C. vulagaris is well taken, however, all these are Caenorhabditis ced-3 and based on that a scope of enablement to nematode ced-3 has been noted in the office action. It is noted that there is no evidence whether a ced-3 gene existed in another organism, other than nematode and even if it existed, it is not clear whether its characteristics would be same as those of a nematode gene. Therefore, the sequence characteristics, domains, mutations, etc of nematode ced-3, disclosed on pages 7 and 8 are not relevant to and can not be relied upon for making changes in a putative ced-3 of any other organism, since there is no evidence in the art or in the specification that any other organism had ced-3 genes and what were their characteristics. As noted in the previous office action, change of even one amino acid in a protein may be make a protein non-functional if the amino acid is crucial for the function of the protein and that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein.

Applicants further argue that the specification teaches methods for isolation of structurally and functionally related ced-3 genes, however, it is noted that the

disclosure in the specification is a general description of the art and there is no specific information regarding the existence of ced-3 gene in any other organism and any characteristic of such a gene or protein. Applicants also argue that that functionally important region can be identified by mutagenesis and that the specification discloses functionally important features of the genes and gene products. However, as discussed above, it is reiterated that the functional regions disclosed (hydrophilic nature and serine rich domains) are not characteristic of the ced-3 genes. Therefore, using these characteristics for isolating other sequences would not yield related proteins. Finally applicants argue that the specification recognizes differences between vertebrate and C. elegans cell death, however there are similarities such as gene activation. Applicants further argue that vertebrate bcl-2 is related to nematode ced-9 and since ced-9 antagonizes the activities of ced-3 and ced-4, bcl-2 interacting proteins would be similar to ced-3. However, gene activation is a very broad term and there is no evidence of record whether same genes would be activated during apoptosis of a nematode cell and a vertebrate cell. It is reiterated that at the time of the invention, state of the art of programmed cell death did not teach ced-3 related genes in other organisms. Therefore, an artisan would have depended on the specification to make and use proteins encoded by ced-3 nucleic acids from other organisms. However, the specification does not teach as to how an artisan of skill would have made a proteins or the nucleic acids that encoded the claimed proteins, encompassed by the claimed invention, from any living organisms? Even if one had to assume that using various screening and other molecular biology techniques described in the specification and available in prior art, an artisan would have been able to isolated a DNA that encoded a protein as encompassed by the claimed invention, an artisan would not be able to know whether the proteins would have a specific functions or a cell death activity and how to use it?

Applicants have further argued that proteins that do not function in the bioassay would not be ced-3 related gene is not persuasive because the issue raised in the previous office action was: results obtained from in vitro or in vivo bioassay system of ced-3 mutant C. elegans may not be useful in determining the

biological activity of a protein in another organism wherein the protein was functionally related to ced-3. Therefore, an artisan would have to develop assay system to test the claimed proteins of the instant application. The specification does not provide any guidance as to how an artisan would have determined what would have been the function of all these polynucleotides and how would these multitude of polynucleotide would have been used or for what use.

In conclusion, the specification as filed is not enabling for the claimed invention commensurate with the scope of the claims and therefore, limitation of the scope of the invention to an isolated ced-3 protein from a nematode, wherein the nematode is a Caenorhabditis elegans, C.briggsae, and C.vulgaris and wherein the protein is encoded by a ced-3 nucleic acid of a Caenorhabditis elegans, C.briggsae, or C.vulgaris, is proper and maintained.

7. Claims 5, 16, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 11-16-01.

Response to Arguments

Applicant's arguments filed 1-31-01 have been fully considered but they are not persuasive. Applicants argue that they teach that they have disclosed ced-3 genes from C. elegans, C. briggsae and C. vulagaris, however, these are all Caenorhabditis species and therefore only represent species of a subgenus, however, the claimed invention as recited encompasses ced-3 of a very large genus and therefore, the description of the Caenorhabditis genes is not a representative a ced-3 nucleic acid would be hydrophilic in nature and would have serine rich domain. However, the hydrophilic nature of ced-3 is not a specific characteristic because if not all most proteins would have this characteristic. Likewise, serine rich domain is not a characteristic specific to ced-3 either, rather would be a common

feature in several proteins. It is noted that any serine kinase would have these characteristics. Furthermore, the specification does not teach characteristics that would distinguish nematode ced-3 from ced-3 of other animal species. Applicants further argue that they teach ced-3 mutations in table 3 and figure 4, that analysis of these mutations identifies highly conserved region of functional importance and that ced-3 proteins are hydrophilic based on protein's hydrophobicity, however, as discussed above these characteristics of nematode genes and there is no evidence of record to indicate as to what would be the identifying/distinguishing characteristics of ced-3 that would determine as to which species of animal they are derived from.

In conclusion, the limited information disclosed in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the ced-3 protein sequence as encompassed by the instantly recited claim. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 19 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because they recite the phrase "structurally related" for reasons of record set forth in the previous office action of 11-16-01.

Applicants have argued that on page 13, lines 15-20 they have defined the term structurally related. However, the indicated section of the specification only says "some structural similarity" to the nucleotide sequence, which does not clearly disclose as to how related the nucleotide sequences are. The word "some" is a relative word and therefore, the degree of relatedness cannot be ascertained for "some structural similarity".

It is noted that the applicants did not address the following 112 2nd paragraph rejections of claim 19.

Claim 19(b) recites the limitation "the ced-3 nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim because the term "a ced-3 nucleic acid" is not recited in the claim 16(b) before.

Claim 19 is further vague and indefinite because the preamble of the claim recites "an isolated protein encoded by an isolated nucleic acid comprising:" and then embodiments a, b, and c are recited. It is not clear as to how a single isolated nucleic acid could comprise all the three embodiments together.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5, 16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan (1990)(listed in the IDS submitted 9-19-00) for reasons of record set forth in the previous office action of 11-16-01.

Response to Arguments

Applicant's arguments filed 1-31-02 have been fully considered but they are not persuasive. Applicants have argued that Yuan et al fails to clone or describe ced-3, to identify open reading frame, sequence or identify ced-3 encoding nucleic acid or amino acid that comprise ced-3 protein. As noted in the previous office action, Yuan teaches nucleic acid sequences that encode ced-3 protein since DNA cosmids restore the ced-3 phenotype when injected in a ced-3 mutant and that the DNA cosmids are structurally and functionally similar to ced-3. It is reiterated that

Yuan does not teach SEQ ID NO 18, however, since the instant application does not describe how similar nucleic acid has to be to SEQ ID NO 18, any ced-3 nucleic acid would be considered similar to SEQ ID NO 18 and thus their encoded protein would anticipate invention of claim 19. It is further acknowledged that while Yuan does not teach an amino acid sequence, since the ced-3 nucleic acids of Yuan complemented function in ced-3 mutant C.elegans, these nucleic acids encode a protein and therefore, the encoding a ced-3 protein will be considered a natural property of the ced-nucleic acids. Accordingly, it would have been obvious at the time of the invention to an artisan to modify the cosmid of Yuan and express it in a cell to produce ced-3 protein and isolate the encoded ced-3 protein. An artisan would have been motivated to make the protein because it would have been a logical extension of the study of Yuan and the isolated protein could be further characterized and researched. Thus, the claimed invention as a whole was prima facie obvious over the prior art.

12. Claim 6 is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c).

For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER